INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

*I, the undersigned, being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the Application and Complete Specification filed in connection with Application for Patent No.**426/Del/02** dated 3rd **April 2002**.*

Witness my hand this 12th Day of May 2003.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

PRIORITY DOCUMENT
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FORM 1

0426-2

03 APR 2002

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956 of 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **" NOVEL TASTE MASKED COMPOSITIONS OF ERYTHROMYCIN A AND DERIVATIVES THEREOF"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

DUPLICATE

3. Further declare that the inventors for the said invention are

a. RAHUL DABRE

b. NAGAPRASAD VISHNUBHOTLA

c. RAJIV MALIK

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Group Leader – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana).
INDIA.
Tel. No. (91-124) 6343126, 6342001 – 10; 8912501-10
Fax No. (91-124) 6342027

6. Following declaration was given by the inventors in the convention country:

We, RAHUL DABRE, NAGAPRASAD VISHNUBHOTLA, RAJIV MALIK of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a. (RAHUL DABRE)

b. V. Nagaprasad
(NAGAPRASAD VISHNUBHOTLA)

c. Rajiv Malik
(RAJIV MALIK)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)

b. Drawings (3 copies)

c. Statement and Undertaking on FORM – 3

d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. **680848** dated **27.03.2002** on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this **2ND** day of **April, 2002.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
COMPANY SECRETARY

FORM 2

The Patents Act, 1970
(39 of 1970)

0426 DEL 2

COMPLETE SPECIFICATION
(See Section 10)

NOVEL TASTE MASKED COMPOSITIONS OF ERYTHROMYCIN A AND DERIVATIVES THEREOF

DUPLICATE

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

Erythromycin and its derivatives are extremely bitter drugs, which when dissolved even in trace quantities in liquid dosage forms, are often perceived to be unpalatable. They are, however, also the drugs of choice for the treatment of common pediatric infections of the middle ear and the upper respiratory tract as well as certain forms of pneumonia which afflict the elderly. Administration of such drugs to children and the elderly, who are commonly affected by such disorders poses a challenge as they experience difficultly in swallowing solid oral dosage forms. For these patients, drugs are commonly provided in liquid forms such as solutions, emulsions and suspensions which usually permit perceptible exposure of the active drug ingredient to the taste bud.

There is therefore a need to mask the taste of such drugs in order to ensure patient compliance during therapy. Conventional taste masking techniques such as the use of sweeteners, aminoacids and flavouring agents are often unsuccessful in masking the taste of highly bitter drugs and other techniques need to be exploited for effectively masking the taste of these drugs.

One such technique involves the use of cation exchange resins to adsorb amine drugs for taste masking and sustained release. It, however, has limited applicability and is not capable of masking the taste of highly bitter drugs.

Coating of bitter drugs is another method which has been reported for taste masking. This technique is effective only for masking the taste of moderately bitter drugs where the coated particles are formulated as aqueous formulations just before administration or are formulated in a non-aqueous medium. This technique, however, has its limitations as it is technology-intensive and the coated granules are easily ruptured by chewing and compression.

Lipid based micro-encapsulation is another technique used for masking the taste of drugs. This technique requires highly sophisticated hot melt granulation for producing free particles, and may have adverse effects on heat sensitive molecules and restrict drug release adversely.

US Patent number 4,808,411 describes taste masked composition comprising 95% of erythromycin or a derivative thereof and about 5 to about 75% of a carbomer. The drug and carbomer are believed to be held together by the ionic interactions between the amine

group of erythromycin compound and the carbonyl group of the carbomer and the gel properties of the carbomer. These complexes are typically prepared by dissolving the drug in a mixture of acetone and alcohol and adding carbomer in acetone or an acetone / alcohol mixture. Utilization of the aforementioned processes on an industrial scale presents a number of problems, including employee safety, emission of solvent vapours to the environment, and cost.

US Patent No. 5,919,489 describes an aqueous granulation process to over come the limitations of US 4,808,411. It involves the steps of mixing a macrolide antibiotic and a carbomer in a weight ratio of between about 1:10 and about 5:2, wetting the mixture with an aqueous solvent; blending the mixture for a time sufficient to allow formation of macrolide antibiotic-carbomer granules, said blending being accomplished in a vessel having a head space which is maintained at a temperature from about 0° to about 70°C and drying the antibiotic-carbomer granules. Like the US Patent 4,808,411, this patent also uses a carbomer for the taste masking of clarithromycin granules.

It is an object of the present invention to describe a process for preparing taste masked granules of clarithromycin comprising the steps of mixing erythromycin or a derivative thereof, alginic acid or its salts, and other pharmaceutically acceptable excipients followed either by granulation in an aqueous solvent or dispersing the mixture in an aqueous solvent and layering on inert cores such as non- pareil seeds, MCC spheres etc.

The erythromycin derivative used in accordance with the present invention is clarithromycin. Clarithromycin is preferably micronized to reduce the particle size to less than 50μm. The granules thus obtained are dried in a fluid bed dryer.

According to the present invention, clarithromycin and alginic acid are taken in a drug to polymer ratio of 2.5 : 1 to 50:1. More preferably, this ratio is between 10:1 to 30:1.

The inert core used in accordance with the present invention is made up of microcrystalline cellulose, starch, sugar or lactose. Most preferably, they are made up of microcrystalline cellulose and are sold under the trade name of Celphere™ seeds.

The particle size of the inert core used in the composition was very critical in determining the taste masking and palatability of the composition. If the particle size was too small, it

resulted in the generation of fines and hence ineffective masking of the taste and if the particle size was large, it resulted in a gritty formulation. The particle size of the composition was therefore kept in the range of from 50 microns to 1000 microns. Preferably the particle size was kept at between 100 microns to 400 microns.

The drug-polymer mixture together with other pharmaceutically acceptable excipients is loaded onto the inert core using a fluid bed processor. The granules thus obtained are dried to a loss on drying of not more than 4.0% at 105°C.

In another embodiment of this invention the drug polymer mixture is granulated using an aqueous media. The granules further comprise other pharmaceutically acceptable excipients selected from amongst binders and disintegrants.

Binders are added to add cohesiveness to the coating composition. Various binders of differing adhesive strength are known in the art. The binders to be used in accordance with the present invention may be selected from amongst those commonly known in the art, such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, pregelatinized starch, gelatin, sucrose and gums such as xanthan gum, gellan gum and the like. The binder is present at a drug to binder ratio of from about 4:1 to about 1:4.

In order to release all the drug quickly upon ingestion, it was necessary to add disintegrants to the formulation. These can be selected from amongst those commonly known in the art such as croscarmellose sodium, cross-linked polyvinylpyrrolidone, sodium starch glycolate, sodium carboxymethylcellulose, starch and the like.

The examples given herein further illustrate the effectiveness of our formulation in achieving both taste masking and optimal dissolution of the drug from the matrix.

Table 1

Ingredient	Amount			
	Ex. 1	Ex2	Ex. 3	Ex.4
Avicel 102	250.0	150.0	250.0	250.0
Clarithromycin	250.0	150.0	250.0	250.0
Alginic acid	12.5	30	25.0	--
Hydroxypropyl methylcellulose	61.5	--	61.5	61.5
Hydroxypropyl cellulose	6.15	--	6.15	6.15
Tween 80	--	0.3	--	--
Water	Qs	1300.0	qs	qs
Iron Oxide Yellow	--	1.0	--	--
Ac-di-sol	20	--	20	20

The binder hydroxypropyl cellulose and hydroxypropyl methyl cellulose were dispersed in water together with croscarmellose sodium and alginic acid. Clarithromycin was added to the dispersion optionally together with the addition of isopropyl alcohol. This dispersion was then coated on microcrystalline cellulose (Celphere™) beads in a fluid bed processor to achieve a weight build up of approximately 140%. The granules were dried in a fluid bed dryer.

The effect of complexing clarithromycin with alginic acid was studied. The granules obtained when no alginic acid was used in the composition (Example 4) were highly bitter. However, addition of even small amounts of alginic acid (Examples 1 to 3) was enough to perceptibly reduce the bitterness of the formulation. All the formulation described above released more than 70% of the drug at pH 6.8 at 50 rpm within 45 minutes.

In another embodiment of the present invention the drug was granulated with alginic acid as described in Table 2.

Table 2

Ingredient	Amount (mg)	
	Example 1	Example 2
Clarithromycin	250	250
Sodium alginate	125	62.5
Methocel E5	--	62.5
Crosscarmellose Sodium	15	15
Sucrose	50	50

Clarithromycin, crosscarmellose sodium and sucrose were sifted and granulated with a solution of sodium alginate in water. The taste masked granules obtained were dried in a fluid bed dryer. Once again granules obtained as described in Examples 1 and 2 above were sufficiently taste masked for formulating into a suitable oral dosage form.

To further reduce dissolution of the active drug in the mouth, the complexes provided in accordance with this invention can be polymer coated. A variety of polymeric materials can be employed. Non-limiting examples of such materials include ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose phthalate, shellac, methacrylate polymers such as those sold under the tradename Eudragit™ E100, S100 and L-100 available from Rohm and Haas Company. Most preferable is hydroxypropyl methylcellulose phthalate. The use of pH sensitive coatings such as Eudragits™ have particular advantage in the case of acid labile drugs such as clarithromycin as they are insoluble in acid or water while dissolving in neutral buffer above pH 5 or 6. This offers the opportunity to prepare a suspension of coated clarithromycin – polymer granules that remain intact in the stomach yet liberate the antibiotic in the intestine thereby protecting the drug from the hostile environment of the stomach and liberating the drug rapidly in the higher pH of the intestinal tract.

The taste masked granules thus obtained may be mixed with flavouring agents such as natural or artificial flavours, citric and tartaric acids. Sweetners such as saccharin and aspartame, and with other pharmaceutically acceptable excipients to be formulated as conventional whole, chewable, dispersible tablets, dry syrup, suspensions, sachets or any other suitable oral dosage form.

WE CLAIM :

1. A process for the preparation of taste masked granules of erythromycin A or derivative thereof comprising the steps of mixing erythromycin A or a derivative thereof, alginic acid or its salts, and other pharmaceutically acceptable excipients followed either by granulation in an aqueous solvent or dispersing the mixture in an aqueous solvent and layering on an inert core.

2. A process as described in claim 1 wherein the erythromycin A derivative is clarithromycin

3. A process as described in claim 2 wherein the particle size of clarithromycin is less than 50 μm.

4. A process as described in claim 1 wherein the weight ratio of clarithromycin to alginic acid is between from about 2.5:1 to about 50:1.

5. A process as described in claim 4 wherein the clarithromycin to alginic acid ratio is preferably between 10:1 to 30:1.

6. A process as described in claim 1 wherein the inert core are made up of microcrystalline cellulose, starch, sugar or lactose.

7. A process as described in claim 6 wherein the inert cores are most preferably made up of microcrystalline cellulose and or sucrose.

8. A process as described in claim 1 wherein the particle size of the inert core is from about 50 microns to 1000 microns.

9. A process as described in claim 8 wherein the particle size of the inert core is preferably from about 100 microns to 400 microns.

10. A process as described in claim 1 wherein the pharmaceutically acceptable excipients are selected from amongst binders and disintegrants.

11. A process as described in claim 10 wherein binders are selected from amongst hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, pregelatinised starch, gelatin, sucrose and gums such as xanthan gum, gellan gum and the like.

12. A process as described in claim 10 wherein the disintegrants are selected from amongst crosscarmellose sodium, sodium starch glycolate, cross-linked polyvinyl pyrrolidone, sodium carboxymethylcellulose, starch and the like.

13. A process as described in claim 1 wherein the taste masked granules are coated.

14. A process as described in claim 1 wherein the taste masked granules are mixed with sugar and artificial sweeteners and / or flavouring agents.

15. A process as described in claim 1 wherein the taste masked granules are formulated as dry syrups, suspensions, conventional whole, chewable, dispersible tablets or any other suitable oral dosage form.

16. A process as described and exemplified herein.

Dated this 2ND day of **April, 2002.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

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